UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,819	01/17/2001	Christopher J. Stanley	PM 275510 P5642US	5588

909 7590 05/20/2003

PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,819	STANLEY, CHRISTOPHER J.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 January 2001 (original)* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/313,385* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's RCE and the amendment filed on February 13, 2003 have been entered. The claims pending in this application are claims 1-22. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on February 13, 2003.

Claim Objections

2. Claims 1, 18, and 21 are objected to because of the following informality: "80,000" should be "80,000 daltons" since unit of a molecular weight is daltons.

3. Claims 2 and 3 are objected to because of the following informality: "macro molecule" in line 2 of claims 2 and 3 should be "macromolecule".

4. Claim 5 is objected to because of the following informalities: (1) "claimed claim 4" should be "claimed in claim 4"; and (2) "40,000,00" should be "4,000,000 daltons" since unit of a molecular weight is daltons.

5. Claim 7 is objected to because of the following informality: "macro molecule" in line 2 of the claim should be "macromolecule".

6. Claims 10 and 14 are objected to because of the following informality: in order to better define the primer which is ligated to said primer and is different from said primer, the examiner suggests that applicant changes "further primer" to "another primer".

7. Claim 20 is objected to because of the following informality: in order to better define said extend primer, examiner suggests that applicant changes the phrase "said extended primer having a sequence complementary to said sequence to be detected bound to said carrier macromolecule" to "said extended primer that has a sequence complementary to said sequence to be detected and is bound to said carrier macromolecule".

Appropriate correction is required.

Specification

8. The examiner notes that there is Figures 1 a and 1 b in this instant application. However, the specification does not have Brief Description of the Drawings which is required by MPEP § 608.01(f) and 37 CFR 1.74.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 1 recites the limitation "said primer" in the claim. There is insufficient antecedent basis for this limitation in the claim since the claim does not describe a primer before the phrase "said primer" appears. The examiner suggests that applicant changes "said primer" to "a primer".

12. Claim 15 recites the limitation "the extended primer" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no extended primer in claims 1-7, 10, and 14. Please clarify.

13. Claim 17 recites the limitation "said biological sample" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no biological sample in claims 1-7, 10, and 14. Since claim 16 has a biological sample, claim 17 should depend on claim 16 and does not depend on claim 14. Please clarify.

14. Claim 18 is rejected as vague and indefinite because the preamble and content of the claim do not correspond each other. Although the claim is directed to a method of detecting the presence of a nucleic acid bound to a carrier macromolecule, there is no carrier macromolecule in the content of the claim. The examiner suggests that applicant adds the phrase "carrier macromolecule" into the content of the claim.

15. Claim 19 is rejected as vague and indefinite in view of the phrase "detecting the presence of said replicated template bound to the carrier macromolecule by a method as claimed in Claim 18" because, although claim 18 is directed to a method of detecting the presence of a nucleic acid bound to a carrier macromolecule, there is no carrier macromolecule in the content of claim 18. In this situation, it is unclear whether the method in claim 18 can be used to detect the presence of a

nucleic acid bound to a carrier macromolecule as recited in claim 19. If applicant adds the phrase "carrier macromolecule" into the content of claim 18, the examiner may withdraw this rejection.

16. Claim 20 recites the limitation "the extended primer" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no extended primer in claim 1.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

18. Claims 18 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Houtz (US Patent No. 5,908,972, filed on July 29, 1996).

The invention is directed to a method of detecting the presence of a nucleic acid bound to a carrier macromolecule and an immobilized nucleic acid. Claim 18 requires that a first nucleic acid having a molecular weight in excess of 80,000 contacts a second nucleic acid having a molecular weight in excess of 80,000 under hybridization conditions and detects hybridization between said first and second nucleic acids. Claim 21 requires that an immobilized nucleic acid

comprising a nucleic acid linked via a covalent bond to a carrier macromolecule having a molecular weight in excess of 80,000 wherein the macromolecule is bound to a solid support.

Houtz teaches isolated spinach ribulose-1,5-bisphosphate carboxylase/oxygenase large subunit/epsilon N-methyltransferase. As shown in Figure 5, an aliquot of 20 μg of spinach genomic DNA was digested with ScaI and EcoRI respectively, electrophoresed on a 0.7% agarose gel and processed for DNA Southern blot analysis by hybridization to a labeled rbcMT-S cDNA probe I (see figure legend of Figure 5 in columns 5 and 6, and column 13) wherein rbcMT-S cDNA probe I was 1056 bp (see lines 19-27 in column 11). Probe I detected a predicted major 2424-bp EcoRI fragment and three ScaI fragments including a 876-bp fragment (see lines 47-52 in column 13 and lines 1-7 of column 14) wherein Figure 5 showed a hybridization pattern of the Southern blot.

Regarding claim 18, since it is known in the art that a base of a single stranded DNA molecule is 325 daltons (see attachment) and hybridization probe and hybridization nucleic target become single strand before they hybridize each other in a hybridization assay, molecular weights of 1056 bp single stranded rbcMT-S cDNA probe I and 2424-bp single stranded EcoRI fragment detected by the hybridization assay are 343,200 daltons and 787,800 daltons respectively (in excess of 80,000 daltons). Since 1056 bp single stranded rbcMT-S cDNA probe I hybridizes with a 2424-bp fragment in EcoR I digested spinach genomic DNAs, single stranded rbcMT-S cDNA probe I and a 2424-bp single stranded EcoR I fragment detected by the hybridization assay are first and second nucleic acids having a molecular weight in excess of 80,000 daltons as recited in claim 18 respectively.

Regarding claim 21, since it is known in the art that a base of a single stranded DNA molecule is 325 daltons (see attachment) and hybridization probe and hybridization nucleic target must become single strand before they hybridize each other in a hybridization assay, molecular weight of 876-bp single stranded ScaI fragment detected by the hybridization assay is 285,350 daltons. Since a nucleic acid can be as a carrier macromolecule, if , in 876-bp single stranded ScaI digested fragment, the first 438 bp is considered as a nucleic acid and the second 438 bp with a molecular weight of 142,675 daltons is considered as a carrier macromolecule, 876-bp single stranded ScaI fragment detected by the hybridization assay is a nucleic acid comprising a nucleic acid linked via a covalent bond to a carrier macromolecule having a molecular weight in excess of 80,000 daltons as recited in claim 21 since the first 438 bp and the second 438 bp in 876-bp ScaI digested fragment is connected by a covalent bond (ie., phosphodiester bond). Since 876-bp ScaI digested fragment is immobilized on a nylon membrane (see lines 10-27 in column 11), 876-bp ScaI digested fragment is an immobilized nucleic acid wherein the macromolecule (ie, the second 438 bp in 876-bp single stranded ScaI digested fragment) is bound to a solid support (ie, a nylon membrane).

Therefore, Houtz teaches all limitations recited in claims 18 and 21.

19. Claims 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Stephens *et al.,* (J. Biol. Chem., 266, 21839-21845, 1991).

The invention is directed to an immobilized nucleic acid and a method of using the immobilized nucleic acid. Claim 21 requires that an immobilized nucleic acid comprising a nucleic

acid linked via a covalent bond to a carrier macromolecule having a molecular weight in excess of 80,000 wherein the macromolecule is bound to a solid support. Claim 22 requires to formulate the immobilized nucleic acid recited in claim 21 as a primer or as a hybridization probe and introduce the immobilized nucleic acid into a hybridization or amplification reaction.

Stephens *et al.*, teach transcriptional repression of the GLUT4 and C/EBP genes in 3T3-L1 adipocytes by tumor necrosis factor-α. Figure 5 demonstrated the hybridization of *in vitro* transcripted RNA to the cDNAs immobilized on nylon membranes in run-on transcription assays (see second paragraph in right column of page 21842 and figure legend of Figure 5 in left column of page 21843) wherein cDNAs comprised 1.7 kb C/EBP, 2.7 kb GLUT1, 2.8 kb GLUT4, 0.8 kb 422, and 1.9 kb β actin (see fifth paragraph in right column of page 21840).

Regarding claim 21, since it is known in the art that a base of a single stranded DNA molecule is 325 daltons (see attachment) and hybridization probe and hybridization nucleic target must be single strand before they hybridize each other in a hybridization assay, molecular weight of 1.7-kb single stranded C/EBP cDNA immobilized on the nylon membrane is 552,550 daltons. Since a nucleic acid can be as a carrier macromolecule, if , in 1.7-kb single stranded C/EBP cDNA, the first 0.85-kb is considered as a nucleic acid and the second 0.85-kb with a molecular weight of 276,250 daltons is considered as a carrier macromolecule, 1.7-kb single stranded C/EBP cDNA immobilized on the nylon membrane is a nucleic acid comprising a nucleic acid linked via a covalent bond to a carrier macromolecule having a molecular weight in excess of 80,000 daltons as recited in claim 21 since the first 0.85-kb and the second 0.85-kb in 1.7-kb single stranded C/EBP cDNA is connected by a covalent bond (ie., phosphodiester bond). Since

1.7-kb single stranded C/EBP cDNA is immobilized on a nylon membrane, 1.7-kb single stranded C/EBP cDNA is an immobilized nucleic acid wherein the macromolecule (ie, the second 0.85-kb in 1.7-kb single stranded C/EBP cDNA) is bound to a solid support (ie, a nylon membrane).

Regarding claim 22, since cDNAs immobilized on the nylon membrane in run-on transcription assays are used as probes to hybridize with *in vitro* transcripted RNA, claim 22 is anticipated by Stephens *et al.*.

Therefore, Stephens *et al.*, teach all limitations recited in claims 21 and 22.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Landegren *et al.*, (US Patent No.4,988,617, published on January 29, 1991) in view of Matteucci *et al.*.(US Patent No. 5,434,257, published on July 18, 1995).

The invention is directed to a process for the replication of a nucleic acid template. Claim 1 requires that a primer that is bonded to a carrier macromolecule and has a molecular

weight in excess of 80,000 hybridizes a nucleic acid template and extending said primer to replicate said template in complementary form. Claim 2 further limits the carrier macromolecule as a natural or synthetic polysaccharide, homopolyamino acid, a natural or synthetic polypeptide or protein, or a synthetic polymer having nucleophilic functional groups (for examples of the carrier macromolecule recited in claim 2, see page 8 of the specification).

Landegren *et al.*, teach method of detecting a nucleotide change in nucleic acids. This method comprised following steps: (a) annealing a labeled oligonucleotide target probe of predetermined sequence to a first sequence of a test substance so that said target nucleotide position was aligned with a nucleotide in an end region of the target probe; (b) annealing a labeled adjacent oligonucleotide probe of predetermined sequence to a second sequence of said test substance contiguous to said first test substance sequence, so that the end region of said target probe was directly adjacent to said adjacent probe; (c) contacting said annealed target and adjacent probes with a linking agent such as a ligase under conditions such that the directly adjacent ends of said probes would link to form a linked probe product unless there was nucleotide base pair mismatch between the target probe and test substance at the target nucleotide position; (d) separating said test substance from said annealed probes, and (e) detecting whether or not linking occurs as an indication of nucleotide base pair matching or mismatching at said target nucleotide position (see Figure 1 and column 3, lines 1-20). These labels on oligonucleotide target and adjacent probes were radioactive tags, enzymes, fluorescent tags, and colorimetric tags (see column 8, lines 43-46) and these labels were exchangeable.

Regarding claims 1 and 2, since the labeled oligonucleotide target probe hybridizes with the target probe in the test substance, the oligonucleotide target probe, the label, and the target probe are a primer, a carrier macromolecule, and a nucleic acid template as recited in claim 1. Since the linked probe product formed by ligating the labeled oligonucleotide target probe and the labeled adjacent oligonucleotide probe hybridizes with the target nucleic acid in the test substance, the process of ligating the labeled oligonucleotide target probe and the labeled adjacent oligonucleotide probe is the step of extending said primer to replicate said template in complementary form as recited in claim 1. Since the label includes a enzyme and the enzyme is a polypeptide or protein, the enzyme label taught by Landegren *et al.*, is said carrier macromolecule as recited in claim 2.

Landegren *et al.*, do not directly show that the label (ie. an enzyme) has a molecular weight in excess of 80,000. However, it is known in the art, a lot of enzymes that are used to label nucleic acid have a molecular weight in excess of 80,000.

Matteucci *et al.*, teach that different kind of compounds such as enzymes are used to covalently label nucleic acids (column 11, third paragraph) wherein at least one of enzymes, alkaline phosphatase is known to have a molecular weight in excess of 80,000.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 1 using a primer bound with a carrier macromolecule having a molecular weight in excess of 80,000 (ie., an enzyme) in view of the patents of Landegren *et al.*, and Matteucci *et al.*. One having ordinary skill in the art would have been motivated to do so because both Landegren *et al.*, and Matteucci *et*

al.., have successfully used an enzyme to label a nucleic acid probe and the simple replacement of one well nucleic acid labeling method from another well known nucleic acid labeling method (i.e., using an enzyme with a molecular weight in excess of 80,000 to label a nucleic acid) during the process for the replication of a nucleic acid template would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

22. No claim is allowed.

23. Claims 3-17 and 20 appears to be allowable if applicant can rewrite in independent form including all of the limitations of the base claim and can overcome the rejections under 35 USC 112, second paragraph since these claims are free of prior art.

24. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
May 16, 2003

Attachment
for office action on 5/16/2003

Calculating molecular weight of nucleic acids (Adapted from Ausubel et al., 1988)

For molecular weight of	Use this calculation
DNA base pair (sodium salt)	1 base pair = 665 daltons
double-stranded DNA molecule	(number of base pairs) x (665 daltons/base pair)
single-stranded DNA molecule	(number of bases) x (325 daltons/base)
single-stranded RNA molecule	(number of bases) x (340 daltons/base)
oligonucleotide	For **dephosphorylated** oligonucleotides: [(number of A x 312.2) + (number of G x 328.2) + (number of C x 288.2) + (number of T x 303.2)] – 61 For **phosphorylated** oligonucleotides: [(number of A x 312.2) + (number of G x 328.2) + (number of C x 288.2) + (number of T x 303.2)] + 17

Conversions between picomoles and micrograms of DNA

For double-stranded DNA (dsDNA):

To convert	Calculate *
pmol to µg	$\text{mol} \times N \times \frac{660\text{pg}}{1\text{pmol}} \times \frac{1\mu\text{g}}{10^6\text{pg}} = \mu\text{g}$
µg to pmol	$\mu\text{g} \times \frac{10^6\text{pg}}{1\mu\text{g}} \times \frac{\text{pmol}}{660\text{pg}} = \text{pmol}$

* N = number of base pairs in DNA; 660, average molecular weight of a base pair.

For single-stranded DNA (ssDNA):

To convert	Calculate *
pmol to µg	$\text{pmol} \times N \times \frac{330\text{pg}}{\text{pmol}} \times \frac{1\mu\text{g}}{10^6\text{pg}} = \mu\text{g}$
µg to pmol	$\mu\text{g} \times \frac{10^6\text{pg}}{1\mu\text{g}} \times \frac{\text{pmol}}{330\text{pg}} \times \frac{1}{N} = \text{pmol}$

* N = number of nucleotides in DNA; 330, average molecular weight of a nucleotide